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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61F 2/06		A1	(11) International Publication Number: WO 00/45744 (43) International Publication Date: 10 August 2000 (10.08.00)
(21) International Application Number: PCT/US00/00717			(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 12 January 2000 (12.01.00)			
(30) Priority Data: 09/243,580 3 February 1999 (03.02.99) US			
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(54) Title: SURFACE PROTECTION METHOD FOR STENTS AND BALLOON CATHETERS FOR DRUG DELIVERY			
(57) Abstract			
<p>A medical device, such as a stent or balloon of a balloon catheter which includes a body portion which has an exterior surface which contacts, at least in part, a vessel wall during treatment. The body portion is expandable from a first position, wherein the body portion is sized for insertion into the vessel lumen, to a second position, wherein at least a portion of the exterior surface is in contact with the lumen wall. The medical device includes a first coating disposed over at least a portion of the exterior surface of the body portion with the first coating including a drug or therapeutic substance which is intended for controlled release from the surface. The medical device further includes a second coating overlying at least a substantial portion of the first coating. The second coating includes a material that is generally impervious to elution of the drug or therapeutic substance therethrough when the body portion is in a first position when inserted into the vessel lumen. The material of the second coating is relatively inelastic so that the second coating fractures during expansion of the body portion to the second position to allow elution of therapeutic substance through a multiplicity of fissures formed through the second coating.</p>			

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**SURFACE PROTECTION METHOD FOR STENTS AND BALLOON
CATHETERS FOR DRUG DELIVERY**

Field of the Invention

The present invention pertains to medical apparatus, particularly expandable
5 stents, having a surface coating applied over a portion of the apparatus' surface. In
particular, the present invention relates to a generally impermeable surface coating which
protects therapeutic materials disposed under the surface coating from the surrounding
environment until the release of these materials is desired and achieved through fracture
of the surface coating.

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Background of the Invention

While angioplasty has gained wide acceptance, abrupt closure and restenosis have
been identified as possible subsequent occurrences. Abrupt closure refers to the acute
occlusion of a vessel immediately after or within the initial hours following a dilation
procedure. Abrupt closure can result in myocardial infarction if blood flow is not
15 restored in a timely manner. The primary mechanisms of abrupt closures are arterial
dissection and/or thrombosis. Restenosis refers to the re-narrowing of an artery after an
initial successful angioplasty. Restenosis occurs primarily within the initial six months
after angioplasty, and is believed due to the proliferation and migration of the cellular
components of the arterial wall.

20

Endovascular stents are placed in the dilated segment of a vessel lumen to
mechanically block the effects of abrupt closure and restenosis. In U.S. Patent No.
5,514,154, Lau et al. disclose an expandable stent which is relatively flexible along its
longitudinal axis. This flexibility facilitates delivery of the stent through tortuous body

lumens. Additionally, the stent is stiff and stable enough radially, in an expanded condition, to maintain the patency of a body lumen such as an artery when implanted therein. Such stents have not, however, eliminated abrupt closure and have not eliminated restenosis.

5 Recent developments have led to stents which attempt to provide anti-thrombogenic and other medications to regions of a blood vessel which have been treated by angioplasty or other interventional techniques. In U.S. Patent No. 5,464,650, Berg et al. disclose a method for making an intravascular stent by applying to the stent, and in particular to its tissue-contacting surface, a solution which includes a solvent, a polymer dissolved in the solvent, and a therapeutic substance dispersed in the solvent. After the solution is applied to the stent, the solvent is then evaporated leaving the polymer/therapeutic agent surface treatment. Berg et al. assert that these devices are capable of providing both short term medication delivery, over the initial hours and days after the treatment, as well as long term medication delivery, over the weeks and months 10 after the treatment.

15

An ongoing problem with present drug release coatings applied to devices such as stents is achieving a therapeutic concentration of a drug locally at a target site within the body without producing unwanted systemic side effects. Implantation of vascular stents is a prime example of a situation where local therapy is needed with drugs that also 20 produce unwanted systemic side effects. Because the stent is placed within a flowing blood stream, during placement and upon implantation, potential unwanted systemic effects may result from undesirable quantities of the therapeutic substance entering the blood stream. Further, if quantities of therapeutic substance are released into the blood

stream during positioning of the stent, less is available for actual local treatment when the stent is expanded, resulting in potential inadequate local dosing. The many attempts to effectuate local drug delivery via endovascular means have failed to address controlling of release of the therapeutic substance systemically during implantation and following 5 implantation.

Therefore, there exists a need in the art for a means and a method for providing local therapy which can sustain high local concentrations of therapeutic drugs at a predetermined site without producing unwanted side effects, such as unwanted quantities of the drugs entering the blood stream. There especially exists a need to provide 10 adequate concentration of therapeutic agents directly to the boundary layer of blood flow near the vessel wall at a targeted treatment area which greatly reduces the systemic side effects and amount of drug needed to achieve a therapeutic result.

Summary of the Invention

The present invention provides a medical device, and a method for manufacturing 15 the medical device, which includes a thin layer overlying a releasable drug or therapeutic substance layer. The thin overlying layer protects the drug layer during positioning and deployment of the medical device within a body lumen. The thin overlying layer is selected to be of a polymeric material and selected thickness which essentially prevents 20 elution of the therapeutic substance until the medical device is placed at a desired location within the body lumen and expanded. The expansion of the medical device produces fissures throughout the overlying layer through which the therapeutic substance elutes. With this design, the therapeutic substance is assured to be applied at the local

selected delivery site with substantially reduced systemic effect from the drug entering the blood stream and traveling away from the deployment site.

The present invention is useful in conjunction with local delivery of drugs or therapeutic substances on an expandable stent within the vascular system. The invention 5 may also be utilized in conjunction with drug delivery from balloon catheters or stents for use in other body lumens. The invention is particularly useful when utilizing a water soluble drug or therapeutic substance which tends to dissolve and migrate within a blood or other body fluid environment. It is also beneficial to use the overlying protective coating when the drug is placed on the medical device with a hydrophilic polymeric 10 carrier, which is intended to dissolve and release the drug or therapeutic substance over an extended period of time when the device is placed within the body lumen at a selected site. The second or overlying layer of protective material, which fractures upon expansion of the medical device, is preferably a biodegradable polymer which is absorbed by the body over an extended period of time, but which prevents elution of the 15 drug or therapeutic substance during the time required to place the device within the vessel lumen.

In preferred embodiments of the present invention, the medical device is one which is designed for treating a vessel lumen wall, such as an arterial wall, in conjunction with treating a stenosis at the same location. The medical device preferably includes a 20 body portion having an exterior surface defined thereon with the body portion being expandable from a first position, wherein the body portion is sized for insertion into the vessel lumen, to a second position, wherein at least a portion of the exterior surface of the medical device is in contact with the lumen wall. A preferred medical device includes a

first coating disposed over at least a portion of the exterior surface of the body portion of the medical device with the first coating including, at least in part, a drug or therapeutic substance for treating the vessel wall. In preferred embodiments, the first coating includes the drug or therapeutic substance in combination with a polymeric carrier which 5 preferably controls the rate of release of the drug or therapeutic substance over an extended period of time. The therapeutic substance or drug releases from the first coating, in preferred embodiments, in response to contact with fluid within the vessel lumen or at the vessel wall.

Preferred drugs or therapeutic substances which may be incorporated into the first 10 coating or included in the first coating with a polymeric carrier include heparin, antibiotics, radiopaque agents, anti-thrombogenic agents, anti-proliferative agents, anti-angiogenic agents, and combinations thereof. Specific drugs can include taxol, taxol derivatives, colchicine, vinblastine or epothilones, which are classified as anti-proliferative and anti-angiogenic agents. A preferred polymeric carrier for the drug or 15 therapeutic substance is a biodegradable agent which can include polylactic acid, polyglycolic acid, polyethylene oxide, polycaprolactones, polydioxanone, poly(orthoesters), polyanhydrides, polyphosphazenes, and mixtures or copolymers of these polymeric materials. The polymeric material could also be selected to include non-biodegradable polymers such as polyurethane, polysiloxane, polyacrylate and mixtures 20 and copolymers of these polymeric materials.

The present invention includes a second coating preferably overlying at least a substantial portion of the first coating. The second coating includes at least in part a material that is generally impervious to elution of the drug or therapeutic substance

therethrough when the body portion of the medical device is in the first position, while being inserted and placed within the lumen. Further, the material of the second coating is preferably relatively inelastic so that the second coating fractures during expansion of the body portion of the medical device to the second position to allow elution of the drug or therapeutic substance through fissures formed through the surface of the second coating. The second coating of the present invention works particularly well in combination with expandable stents or drug delivery balloons. The second coating is preferably a polymeric material which can include polylactic acid, polyglycolic acid, polyanhydrides, polyphosphazenes, poly(orthoesters) and mixtures and copolymers of these polymeric materials. In preferred embodiments, the thickness of the second coating is about 0.01 μ m to about 5 μ m.

A preferred medical device of the present invention includes a stent which is a generally tubular structure having an exterior surface defined by a plurality of interconnected struts having interstitial spaces therebetween. The generally tubular structure is expandable from a first position, wherein the stent is sized for intravascular insertion, to a second position, wherein at least a portion of the exterior surface of the stent contacts the vessel wall. The expanding of the stent is accommodated by flexing and bending of the interconnected struts throughout the generally tubular structure. The second coating overlying the stent surface which protects the therapeutic substance or drug during placement, fractures upon flexing and bending of the struts on the stent during expansion.

The second coating of the present invention can also be utilized on a medical device, such as a balloon catheter, wherein the second coating is included on at least a

portion of the balloon which is expandable from a folded or unexpanded first position to an expanded second position which is adapted for treatment of the vascular lumen wall by contact with at least a portion of the exterior surface of the balloon. The second coating overlying the drug or therapeutic substance is again relatively inelastic so that 5 upon expansion of the balloon, the coating fractures to allow elution of the drug or therapeutic substance through fissures formed in the coating.

Additional features of the invention and the advantages derived therefrom, and the various scopes and aspects of the invention will become apparent from the drawings, the description of the preferred embodiments of the invention, and the claims.

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Description of the Drawings

Fig. 1 is a perspective view of a stent in accordance with an exemplary embodiment of the present invention;

Fig. 2 is a magnified, partial perspective view of FIG. 1 in a first, non-expanded form, illustrating the polymeric surface coating selectively applied to wire members;

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Fig. 3 is a magnified, partial perspective of FIG. 2 in a second, expanded form, illustrating the polymeric fragmentation and subsequent elution of a therapeutic substance arising from the expansion of the stent;

Fig. 4 is a schematic representation of a catheter of the present invention having a folded balloon in a first position thereon inserted within a vessel lumen; and

20

Fig. 5 is a schematic representation of the catheter of Fig. 4 having the balloon in a second expanded position for treatment of the vessel wall.

Detailed Description of the Drawings

Stents of the type shown in Fig. 1, disclosed in U.S. Patent Application Serial No. 08/874,190, filed June 13, 1997, entitled "Polymeric Layered Stents", perform the desired applications of dilating and maintaining the patency of various lumen passages within the 5 human body. The above application is assigned to the assignee of the present invention, and the disclosure is hereby incorporated by reference.

Referring now to the drawings wherein like reference numerals refer to like elements throughout the several views, Fig. 1 shows a perspective view of a stent 10, in a non-expanded form, in accordance with the present invention. The skeletal frame of the 10 stent 10 preferably includes wire-like members 12 forming a distinct, repetitive serpentine pattern. This repetitive serpentine pattern consists of multiple U-shaped curves 14. These U-shaped curves 14 form interstitial spaces 16. With no recognizable beginning or end to this serpentine pattern, wire 12 forms expandable serpentine element 18. Serpentine elements 18 are arranged along the longitudinal axis of the stent 10 so 15 that the U-shaped curves 14 of abutting serpentine elements 18 may be joined through an interconnecting element 20. Through the interconnecting elements 20, a continuous wire 12 framework is created between multiple serpentine elements 18 forming the stent 10.

A surface treatment 30 is selectively applied to the skeletal frame of the stent 10. This surface treatment 30 comprises at least two overlying coatings selectively applied to 20 at least a portion of the exterior surface of the wire-like members 12. The function of the two overlying coatings is best understood from the depictions in Fig. 2 and Fig. 3, as described below.

Referring now to Fig. 2, a portion of the stent of Fig. 1 is depicted in magnified view with the first coating 32 disposed over at least a portion of the exterior surface of wire-like members 12. The first coating 32 includes at least in part, a therapeutic substance or drug. In a preferred embodiment, the therapeutic substance is comprised, at 5 least in part, of an anti-proliferative or anti-angiogenic drug. This therapeutic substance is typically dispersed and contained in a polymeric carrier matrix forming the first coating 32. The use of a matrix allows for a selectively controlled elution rate for the incorporated drug or therapeutic substance. By modifying the ratio of polymeric carrier to therapeutic substance, the ability of the therapeutic substance to elute from the carrier 10 either increases or decreases. In a further preferred embodiment, the elution rate of the therapeutic substance may be controlled by utilizing a biodegradable polymeric carrier. Polylactic acid (PLA), polyglycolic acid, polyethylene oxide (PEO), polycaprolactone are examples of such polymeric carriers. Either the homopolymer or the copolymer forms of these materials may be utilized in the incorporation with the therapeutic 15 substance. Other polymeric carriers which may be utilized include: polyurethane, polysiloxane, polyacrylate and their mixtures or copolymers.

Other therapeutic substances or drugs can also be incorporated into the first coating, either alone or in combination with the anti-proliferative or anti-angiogenic agents. These drugs can include heparin, antibiotics, radiopaque agents and anti- 20 thrombogenic agents.

These components may be added to the anti-proliferative or anti-angiogenic drug in order to alter the function of the therapeutic substance. In a preferred embodiment, to prevent the aggregation of platelets, fibrin, clotting factors, and cellular elements of the

blood as a result of the implementation of the stent 10, the anti-proliferative drug or anti-angiogenic drug may also contain an additional anti-thrombogenic drug that may be incorporated with the other drugs forming the first coating 32. In a further preferred embodiment, the anti-angiogenic drug is Taxol, Taxol derivatives, colchicine, vinblastine, 5 or epothilone.

The second coating 34, preferably the outermost coating, overlays at least a substantial portion of the first, or previous coating 32. This second coating 34 comprises a material that is generally impervious to the elution of the therapeutic substance or drug incorporated in the first coating 32. The second coating 34 acts as a protective coating 10 for the drug or therapeutic substance which prevents the drug or therapeutic substance from elution prior to proper placement within the vessel lumen at a treatment site. Further, this protective layer prevents physical damage to the drug coating layer during 15 insertion. In preferred embodiments, release of the therapeutic substance is enhanced by contact with water or other liquids present in the blood or other body lumen. This is particularly true in embodiments which incorporate a drug or therapeutic substance which 20 is water soluble or a polymeric carrier that is hydrophilic and tends to release more therapeutic substance upon contact with a liquid such as water. Thus, the second coating 34 or overlayer of protective coating is preferably impervious to water or body fluids, at least for the time period required for placement of the stent within the vessel lumen at the treatment site. In this way, the elution of the drug is prevented until the medical device or stent is located at the required treatment site.

Thus, in use, the stent or other medical device of the present invention is coated with first a drug or therapeutic substance, followed by an overlying coat of a second

coating or protective coating. The first coating may be placed on the medical device while in an unexpanded configuration, or alternatively, the device may be expanded for coating and then contracted for placement in the vessel. The second coating, or protective coating, is made to overly the first coating while the medical device is in the 5 first position for insertion in the lumen. In preferred embodiments, the second coating material is relatively inelastic so that the second coating fractures during expansion of the body portion of the medical device to the second position. The portion of the stent depicted in Fig. 2 is depicted in Fig. 3 in an expanded state, which clearly indicates a multiplicity of fractures or fissures 40 throughout the second coating 32 with the drug or 10 therapeutic substance 30 eluting through the fissures 40.

As previously stated, the second coating is preferably a polymeric coating which is relatively inelastic so that the expansion of the stent or other medical device causes fractures to form within the coating surface. These fractures allow the elution of the drug or therapeutic substance therethrough. A preferred polymeric material includes 15 polylactic acid, polyglycolic acid, polyanhydrides, polyphosphazene or poly(orthoester). The thickness of the second coating is preferably about 0.01 μ m to about 5.0 μ m. The second coating is preferably biodegradable or bioabsorbable so that over time the second coating is absorbed by the body.

The present invention has been discussed in conjunction with a preferred stent. 20 However, it is recognized that the invention disclosed herein may be utilized with any stent design which is expanded from a first position to a second position with resultant fracture of a second protective coating thereon. Preferred stents include those generally tubular structures having an exterior surface defined by a plurality of interconnected

struts having interstitial spaces therebetween. In the first position, the stent is sized so that it may be inserted into the lumen of the intravascular system. Once located at a point of treatment, the stent may be expanded to a second position wherein at least a portion of the exterior surface contacts the wall of the vessel lumen.

5 The use of a second protective coating, as described above for a stent, can also be incorporated into a medical device such as a balloon-type drug delivery catheter or balloon dilatation catheter. Figs. 4 and 5 depict the incorporation of the present invention into a balloon catheter design. The materials and therapeutic substances discussed above are equally applicable in the present balloon catheter embodiment.

10 Now referring to Fig. 4, a vessel 50 within the vascular system is depicted schematically with a lumen 52 defined therethrough which is partially occluded by a stenosis 54 therein. The lumen is defined by lumen walls 56 as indicated. A balloon catheter 58 is depicted as being inserted into the vessel lumen 52. The balloon catheter 58 includes a shaft 60 having disposed on a distal portion thereof an inflatable balloon 62.

15 The balloon 62 is depicted in a folded or uninflated profile which is suitable for inserting into the lumen 52 of the blood vessel 50.

20 The balloon 62 includes a drug or therapeutic substance coated on the surface thereof. In preferred embodiments, the entire surface of the balloon is coated with a drug or therapeutic substance, either alone or in a polymeric carrier, while the balloon is in an inflated position so that the entire surface thereof includes the drug or therapeutic substance thereon. The second coating or protective coating is applied while the balloon is in a deflated or low profile condition. Again, this protective coating prevents the

elution of the drug from the surface of the balloon which is exposed during insertion of the catheter prior to inflation of the balloon at the treatment site.

Referring now to Fig. 5, the balloon catheter 58 of Fig. 4 is depicted with the balloon located across the stenotic area 54 in an inflated condition. As shown in Fig. 5, 5 the balloon includes a first coat 30, which includes the drug or therapeutic substance, and a second coat, which is the protective coating which was applied when the balloon was in a deflated condition. Fig. 5 schematically depicts the multiplicity of fissures 40 which are formed in the balloon surface coating 32 upon expansion of the balloon. This results in elution of the drug or therapeutic substance 30 through such fissures into the treatment 10 area.

Numerous characteristics and advantages of the invention covered by this document have been set forth in the foregoing description. It will be understood, however, that this disclosure is, in many aspects, only illustrative. Changes may be made in details, particularly in matters of shape, size, and arrangement of parts without 15 exceeding the scope of the invention. The invention scope is defined, of course, in the language within the appended claims are expressed.

What is claimed is:

1. A medical device for treating a lumen wall comprising:

a body portion having an exterior surface defined thereon, said body portion being expandable from a first position, wherein said body portion is sized for insertion into said lumen, to a second position wherein at least a portion of said exterior surface is in contact with said lumen wall;

a first coating disposed over at least a portion of said exterior surface of said body portion, said first coating comprising at least in part a therapeutic substance; and,

a second coating overlying at least a substantial portion of said first coating, said second coating comprising a material that is generally impervious to elution of said therapeutic substance therethrough when said body portion is in said first position when inserted in said lumen, while being relatively inelastic so that said second coating fractures during expansion of said body portion to said second position to allow elution of said therapeutic substance through fissures formed therethrough.

2. The medical device of claim 1, wherein said device is an expandable stent.

3. The medical device of claim 1, wherein said device is a balloon catheter.

4. The medical device of claim 1, wherein said therapeutic substance releases from said exterior surface in response to fluid contact absent said second coating.

5. The medical device of claim 1, wherein said therapeutic substance is selected from the group consisting of: heparin, antibiotics, radiopaque agents, anti-thrombogenic agents, anti-proliferative agents, anti-angiogenic agents and combinations thereof.
6. The medical device of claim 5, wherein said anti-proliferative and anti-angiogenic agents are selected from the group consisting of: taxol, taxol derivatives, colchicine, vinblastine or epothilone.
7. The medical device of claim 4, wherein said fluid contact includes blood within said lumen.
8. The medical device of claim 1, wherein said first coating further comprises a polymeric carrier having said therapeutic substance dispersed therethrough.
9. The medical device of claim 8, wherein said polymeric carrier is biodegradable.
10. The medical device of claim 9, wherein said polymeric carrier is selected from the group consisting of: polylactic acid, polyglycolic acid, polyethylene oxide, polycaprolactone, polydioxanones, polyanhydrides, polyphosphazenes, poly(orthoesters) and mixtures or copolymers thereof.

11. The medical device of claim 1, wherein said second coating is a polymeric material selected from the group consisting of: polylactic acid, polyglycolic acid, polyanhydrides, polyphosphazenes, poly(orthoesters) and mixture and copolymers thereof.

12. The medical device of claim 11, wherein said second coating of a thickness of about 0.01 μ m to about 5.0 μ m.

13. An intravascular stent adapted for treating a vessel wall comprising:

a generally tubular structure having an exterior surface defined by a plurality of interconnected struts having interstitial spaces therebetween, said generally tubular structure expandable from a first position, wherein said stent is sized for intravascular insertion, to a second position, wherein at least a portion of said exterior surface contacts said vessel wall, said expanding of said generally tubular structure accommodated by flexing and bending of said interconnected struts;

a first coating disposed over at least a portion of said exterior surface of said generally tubular structure, said first coating comprising at least in part a therapeutic substance; and,

a second coating overlying at least a substantial portion of said first coating, said second coating comprising a material that is generally impervious to elution of said therapeutic substance therethrough when said body portion is in said first position within said intravascular lumen, while being relatively inelastic so that said second coating fractures in response to flexing and bending of said struts during expansion to said second

position to allow elution of said therapeutic substance through fissures formed therethrough.

14. The stent of claim 13, wherein said therapeutic substance releases from said exterior surface in response to fluid contact absent said second coating.

15. The stent of claim 13, wherein said therapeutic substance is selected from the group consisting of: heparin, antibiotics, radiopaque agents, anti-thrombogenic agents, anti-proliferative agents, anti-angiogenic agents and combinations thereof.

16. The stent of claim 15, wherein said anti-proliferative and anti-angiogenic agents are selected from the group consisting of: taxol, taxol derivatives, colchicine, vinblastine and epothilone.

17. The stent 14, wherein said fluid contact includes blood within said lumen.

18. The stent of claim 13, wherein said first coating further comprises a polymeric carrier having said therapeutic substance dispersed therethrough.

19. The stent of claim 18, wherein said polymeric carrier is biodegradable.

20. The stent of claim 19, wherein said polymeric carrier is selected from the group consisting of: polylactic acid, polyglycolic acid, polyethylene oxide,

polycaprolactone, polydioxanone, polyanhydrides, polyphosphaenes, poly(orthoesters) and mixtures or copolymers thereof.

21. The stent of claim 13, wherein said therapeutic substance is elutable in contact with water containing fluids absent said second coating.

22. In an intravascular medical device having a body portion with an exterior surface defined thereon, at least a portion of said body portion which is expandable from a folded or unexpanded first position, which is adapted for insertion into a vascular lumen to an expanded second position, which is adapted for treatment of the vascular lumen wall by contact with at least a portion of said exterior surface, the improvement comprising:

a first coating disposed over at least a portion of said exterior surface of said body portion, said first coating comprising at least in part a therapeutic substance; and,

a second coating overlying at least a substantial portion of said first coating, said second coating comprising a material that is relatively inelastic so that said second coating fractures during expansion of said body portion to said second position to allow elution of said therapeutic substance through fissures formed therethrough.

23. The intravascular medical device of claim 22, wherein said therapeutic substance releases from said exterior surface in response to fluid contact absent said second coating.

24. The intravascular medical device of claim 22, wherein said therapeutic substance is selected from the group consisting of : heparin, antibiotics, radiopaque agents, anti-thrombogenic agents, anti-proliferative agents, anti-angiogenic agents and combinations thereof.

25. The intravascular medical device of claim 24, wherein said anti-proliferative and anti-angiogenic agents are selected from the group consisting of: taxol, taxol derivatives, colchicine, vinblastine and epothilones.

26. The intravascular medical device of claim 22, wherein said first coating further comprises a polymeric carrier having said therapeutic substance dispersed therethrough.

27. The intravascular medical device of claim 26, wherein said polymeric carrier is biodegradable.

28. The intravascular medical device of claim 27, wherein said polymeric carrier is selected from the group consisting of: polylactic acid, polyglycolic acid, polyethylene oxide, polycaprolactone, polydioxanone, polyanhydrides, polyphosphazenes, poly(orthoesters) and mixtures or copolymers thereof.

29. The intravascular medical device of claim 22, wherein said therapeutic substance is elutable in contact with water containing fluids absent said second coating.

30. A catheter for drug delivery comprising:

a longitudinally extending shaft having a distal end and a proximal end, the shaft defining an inflation lumen;

a balloon member having an exterior surface defined thereon disposed proximate the distal end of said shaft in fluid communication with said inflation lumen, said balloon member expandable from a first deflated position, wherein said balloon member is sized for intravascular insertion, to a second inflated position, wherein at least a portion of said exterior surface contacts said vessel wall;

a first coating disposed over at least a portion of said exterior surface of said balloon member, said first coating comprising at least in part a therapeutic substance; and,

a second coating overlying at least a substantial portion of said first coating, when said balloon member is in said first deflated position, said second coating comprising a material which is relatively inelastic so that said second coating fractures in response to expansion of said balloon member to said second position to allow elution of said therapeutic substance through fissures formed therethrough.

31. The catheter of claim 30, wherein said therapeutic substance releases from said exterior surface in response to fluid contact absent said second coating.

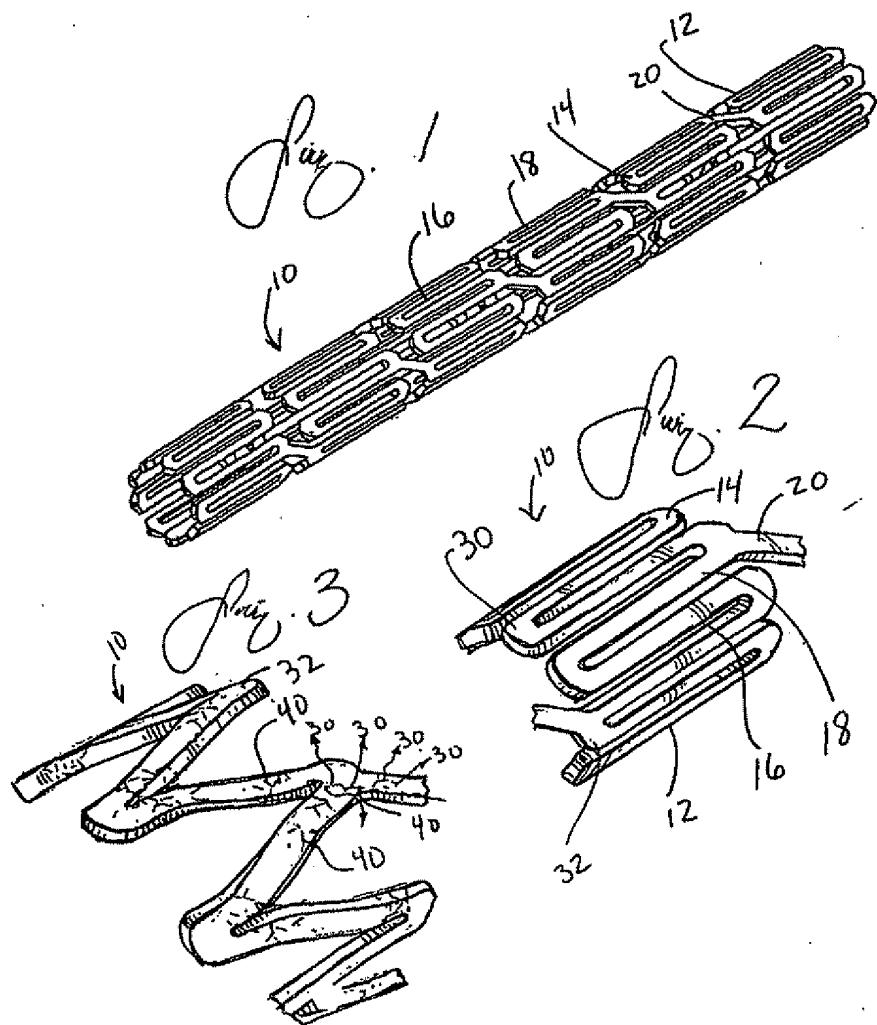
32. The catheter of claim 30, wherein said second coating is a polymeric material selected from the group consisting of polylactic acid, polyglycolic acid,

polyanhydrides, polyphosphazenes, poly(orthoesters) and mixtures and copolymers thereof.

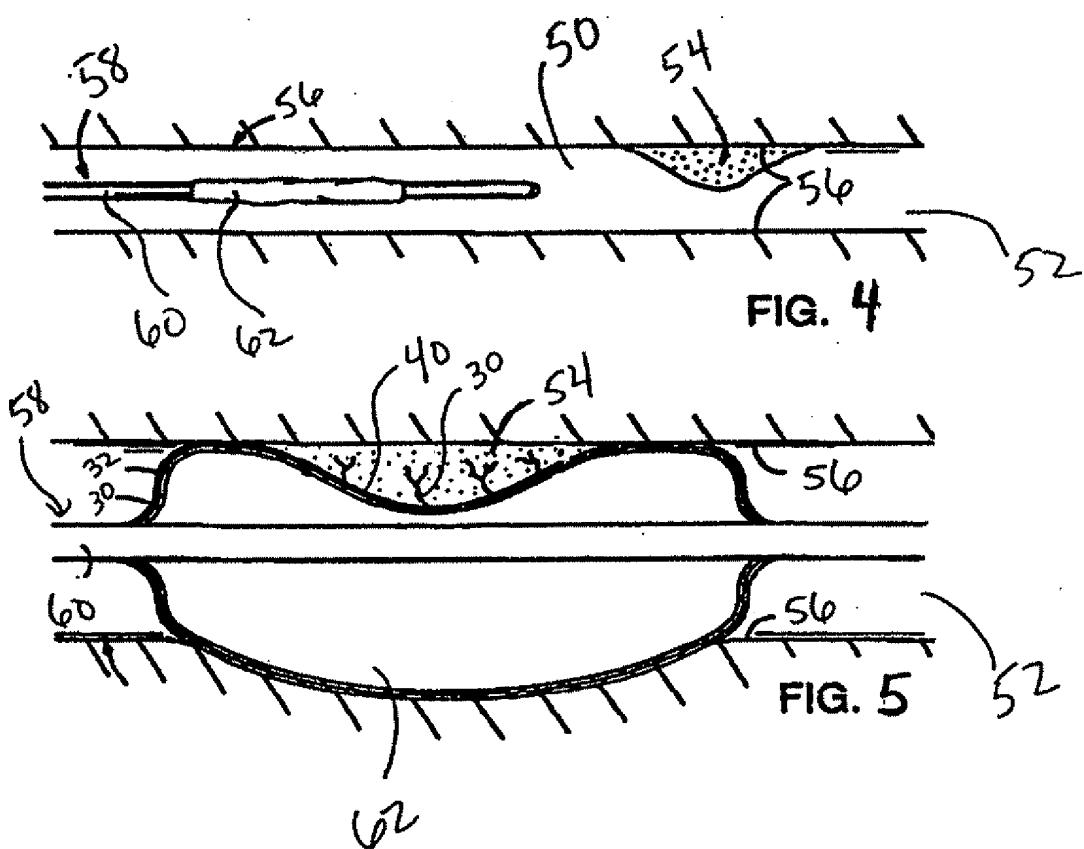
33. The catheter of claim 30, wherein said therapeutic substance is selected from the group consisting of: taxol, taxol derivatives, colchicine, vinblastine and epothilone.

34. The catheter of claim 30, wherein said therapeutic substance is elutable in contact with water containing fluids absent said second coating.

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2/2



INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/00717

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61F2/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 324 261 A (AMUNDSON RODNEY R ET AL) 28 June 1994 (1994-06-28) figures 4,5 column 2, line 51 -column 3, line 2 column 3, line 40 -column 4, line 32 column 4, line 41 -column 6, line 27 claims 1-8	1,3-12, 22-34
A		13-21
Y	US 5 735 897 A (BUIRGE ANDREW W) 7 April 1998 (1998-04-07) column 2, line 37 -column 3, line 45 column 4, line 6 - line 31 column 5, line 26 - line 54 claims 1-58	13
A	----- -----	1,22,30

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

T later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

V document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the International search

Date of mailing of the International search report

16 May 2000

26/05/2000

Name and mailing address of the ISA

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Authorized officer

Mary, C

INTERNATIONAL SEARCH REPORT

International Application No	
PCT/US 00/00717	

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 23228 A (ALZA CORP) 4 June 1998 (1998-06-04) page 6, line 30 -page 8, line 4 page 10, line 1 - line 23 page 13, line 3 -page 14, line 2 -----	13
A		1,22,30
A	US 5 674 241 A (BLEY ROBERT S ET AL) 7 October 1997 (1997-10-07) column 5, line 63 -column 7, line 62 -----	1,13,22, 30
1		

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/00717

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5324261 A	28-06-1994	US 5102402 A		07-04-1992
		US 5370614 A		06-12-1994
		CA 2077539 A		05-07-1992
		DE 69119753 D		27-06-1996
		DE 69119753 T		23-01-1997
		EP 0519063 A		23-12-1992
		IE 78821 B		25-02-1998
		JP 5505132 T		05-08-1993
		WO 9211890 A		23-07-1992
		US 5893840 A		13-04-1999
US 5735897 A	07-04-1998	WO 9510989 A		27-04-1995
WO 9823228 A	04-06-1998	AU 5266698 A		22-06-1998
US 5674241 A	07-10-1997	US 5968070 A		19-10-1999
		AU 4929696 A		11-09-1996
		CA 2213403 A		29-08-1996
		EP 0810845 A		10-12-1997
		WO 9625897 A		29-08-1996

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 August 2000 (10.08.2000)

PCT

(10) International Publication Number
WO 00/45744 A1

(51) International Patent Classification⁷: **A61F 2/06**

(21) International Application Number: **PCT/US00/00717**

(22) International Filing Date: 12 January 2000 (12.01.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 09/243,580 3 February 1999 (03.02.1999) US

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(81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

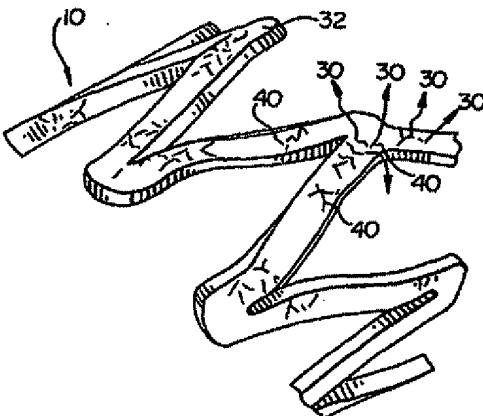
— with international search report

(48) Date of publication of this corrected version:
30 August 2001

(15) Information about Correction:
see PCT Gazette No. 35/2001 of 30 August 2001, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **SURFACE PROTECTION METHOD FOR STENTS AND BALLOON CATHETERS FOR DRUG DELIVERY**



(57) Abstract: A medical device, such as a stent or balloon of a balloon catheter which includes a body portion which has an exterior surface which contacts, at least in part, a vessel wall during treatment. The body portion is expandable from a first position, wherein the body portion is sized for insertion into the vessel lumen, to a second position, wherein at least a portion of the exterior surface is in contact with the lumen wall. The medical device includes a first coating disposed over at least a portion of the exterior surface of the body portion with the first coating including a drug or therapeutic substance which is intended for controlled release from the surface. The medical device further includes a second coating overlying at least a substantial portion of the first coating. The second coating includes a material that is generally impervious to elution of the drug or therapeutic substance therethrough when the body portion is in a first position when inserted into the vessel lumen. The material of the second coating is relatively inelastic so that the second coating fractures during expansion of the body portion to the second position to allow elution of therapeutic substance through a multiplicity of fissures formed through the second coating.

WO 00/45744 A1

**SURFACE PROTECTION METHOD FOR STENTS AND BALLOON
CATHETERS FOR DRUG DELIVERY**

Field of the Invention

The present invention pertains to medical apparatus, particularly expandable 5 stents, having a surface coating applied over a portion of the apparatus' surface. In particular, the present invention relates to a generally impermeable surface coating which protects therapeutic materials disposed under the surface coating from the surrounding environment until the release of these materials is desired and achieved through fracture of the surface coating.

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Background of the Invention

While angioplasty has gained wide acceptance, abrupt closure and restenosis have been identified as possible subsequent occurrences. Abrupt closure refers to the acute occlusion of a vessel immediately after or within the initial hours following a dilation procedure. Abrupt closure can result in myocardial infarction if blood flow is not 15 restored in a timely manner. The primary mechanisms of abrupt closures are arterial dissection and/or thrombosis. Restenosis refers to the re-narrowing of an artery after an initial successful angioplasty. Restenosis occurs primarily within the initial six months after angioplasty, and is believed due to the proliferation and migration of the cellular components of the arterial wall.

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Endovascular stents are placed in the dilated segment of a vessel lumen to mechanically block the effects of abrupt closure and restenosis. In U.S. Patent No. 5,514,154, Lau et al. disclose an expandable stent which is relatively flexible along its longitudinal axis. This flexibility facilitates delivery of the stent through tortuous body

lumens. Additionally, the stent is stiff and stable enough radially, in an expanded condition, to maintain the patency of a body lumen such as an artery when implanted therein. Such stents have not, however, eliminated abrupt closure and have not eliminated restenosis.

5 Recent developments have led to stents which attempt to provide anti-thrombogenic and other medications to regions of a blood vessel which have been treated by angioplasty or other interventional techniques. In U.S. Patent No. 5,464,650, Berg et al. disclose a method for making an intravascular stent by applying to the stent, and in particular to its tissue-contacting surface, a solution which includes a solvent, a polymer dissolved in the solvent, and a therapeutic substance dispersed in the solvent. After the solution is applied to the stent, the solvent is then evaporated leaving the polymer/therapeutic agent surface treatment. Berg et al. assert that these devices are capable of providing both short term medication delivery, over the initial hours and days after the treatment, as well as long term medication delivery, over the weeks and months 10 after the treatment.

15

16 An ongoing problem with present drug release coatings applied to devices such as stents is achieving a therapeutic concentration of a drug locally at a target site within the body without producing unwanted systemic side effects. Implantation of vascular stents is a prime example of a situation where local therapy is needed with drugs that also 20 produce unwanted systemic side effects. Because the stent is placed within a flowing blood stream, during placement and upon implantation, potential unwanted systemic effects may result from undesirable quantities of the therapeutic substance entering the blood stream. Further, if quantities of therapeutic substance are released into the blood

stream during positioning of the stent, less is available for actual local treatment when the stent is expanded, resulting in potential inadequate local dosing. The many attempts to effectuate local drug delivery via endovascular means have failed to address controlling of release of the therapeutic substance systemically during implantation and following 5 implantation.

Therefore, there exists a need in the art for a means and a method for providing local therapy which can sustain high local concentrations of therapeutic drugs at a predetermined site without producing unwanted side effects, such as unwanted quantities of the drugs entering the blood stream. There especially exists a need to provide 10 adequate concentration of therapeutic agents directly to the boundary layer of blood flow near the vessel wall at a targeted treatment area which greatly reduces the systemic side effects and amount of drug needed to achieve a therapeutic result.

Summary of the Invention

The present invention provides a medical device, and a method for manufacturing 15 the medical device, which includes a thin layer overlying a releasable drug or therapeutic substance layer. The thin overlying layer protects the drug layer during positioning and deployment of the medical device within a body lumen. The thin overlying layer is selected to be of a polymeric material and selected thickness which essentially prevents elution of the therapeutic substance until the medical device is placed at a desired 20 location within the body lumen and expanded. The expansion of the medical device produces fissures throughout the overlying layer through which the therapeutic substance elutes. With this design, the therapeutic substance is assured to be applied at the local

selected delivery site with substantially reduced systemic effect from the drug entering the blood stream and traveling away from the deployment site.

The present invention is useful in conjunction with local delivery of drugs or therapeutic substances on an expandable stent within the vascular system. The invention 5 may also be utilized in conjunction with drug delivery from balloon catheters or stents for use in other body lumens. The invention is particularly useful when utilizing a water soluble drug or therapeutic substance which tends to dissolve and migrate within a blood or other body fluid environment. It is also beneficial to use the overlying protective coating when the drug is placed on the medical device with a hydrophilic polymeric 10 carrier, which is intended to dissolve and release the drug or therapeutic substance over an extended period of time when the device is placed within the body lumen at a selected site. The second or overlying layer of protective material, which fractures upon expansion of the medical device, is preferably a biodegradable polymer which is absorbed by the body over an extended period of time, but which prevents elution of the 15 drug or therapeutic substance during the time required to place the device within the vessel lumen.

In preferred embodiments of the present invention, the medical device is one which is designed for treating a vessel lumen wall, such as an arterial wall, in conjunction with treating a stenosis at the same location. The medical device preferably includes a 20 body portion having an exterior surface defined thereon with the body portion being expandable from a first position, wherein the body portion is sized for insertion into the vessel lumen, to a second position, wherein at least a portion of the exterior surface of the medical device is in contact with the lumen wall. A preferred medical device includes a

first coating disposed over at least a portion of the exterior surface of the body portion of the medical device with the first coating including, at least in part, a drug or therapeutic substance for treating the vessel wall. In preferred embodiments, the first coating includes the drug or therapeutic substance in combination with a polymeric carrier which 5 preferably controls the rate of release of the drug or therapeutic substance over an extended period of time. The therapeutic substance or drug releases from the first coating, in preferred embodiments, in response to contact with fluid within the vessel lumen or at the vessel wall.

Preferred drugs or therapeutic substances which may be incorporated into the first 10 coating or included in the first coating with a polymeric carrier include heparin, antibiotics, radiopaque agents, anti-thrombogenic agents, anti-proliferative agents, anti-angiogenic agents, and combinations thereof. Specific drugs can include taxol, taxol derivatives, colchicine, vinblastine or epothilones, which are classified as anti-proliferative and anti-angiogenic agents. A preferred polymeric carrier for the drug or 15 therapeutic substance is a biodegradable agent which can include polylactic acid, polyglycolic acid, polyethylene oxide, polycaprolactones, polydioxanone, poly(orthoesters), polyanhydrides, polyphosphazenes, and mixtures or copolymers of these polymeric materials. The polymeric material could also be selected to include non-biodegradable polymers such as polyurethane, polysiloxane, polyacrylate and mixtures 20 and copolymers of these polymeric materials.

The present invention includes a second coating preferably overlying at least a substantial portion of the first coating. The second coating includes at least in part a material that is generally impervious to elution of the drug or therapeutic substance

therethrough when the body portion of the medical device is in the first position, while being inserted and placed within the lumen. Further, the material of the second coating is preferably relatively inelastic so that the second coating fractures during expansion of the body portion of the medical device to the second position to allow elution of the drug or therapeutic substance through fissures formed through the surface of the second coating.

5 The second coating of the present invention works particularly well in combination with expandable stents or drug delivery balloons. The second coating is preferably a polymeric material which can include polylactic acid, polyglycolic acid, polyanhydrides, polyphosphazenes, poly(orthoesters) and mixtures and copolymers of these polymeric materials. In preferred embodiments, the thickness of the second coating is about 10 0.01 μ m to about 5 μ m.

A preferred medical device of the present invention includes a stent which is a generally tubular structure having an exterior surface defined by a plurality of interconnected struts having interstitial spaces therebetween. The generally tubular structure is expandable from a first position, wherein the stent is sized for intravascular insertion, to a second position, wherein at least a portion of the exterior surface of the stent contacts the vessel wall. The expanding of the stent is accommodated by flexing and bending of the interconnected struts throughout the generally tubular structure. The second coating overlying the stent surface which protects the therapeutic substance or 15 drug during placement, fractures upon flexing and bending of the struts on the stent 20 during expansion.

The second coating of the present invention can also be utilized on a medical device, such as a balloon catheter, wherein the second coating is included on at least a

portion of the balloon which is expandable from a folded or unexpanded first position to an expanded second position which is adapted for treatment of the vascular lumen wall by contact with at least a portion of the exterior surface of the balloon. The second coating overlying the drug or therapeutic substance is again relatively inelastic so that upon expansion of the balloon, the coating fractures to allow elution of the drug or therapeutic substance through fissures formed in the coating.

Additional features of the invention and the advantages derived therefrom, and the various scopes and aspects of the invention will become apparent from the drawings, the description of the preferred embodiments of the invention, and the claims.

10

Description of the Drawings

Fig. 1 is a perspective view of a stent in accordance with an exemplary embodiment of the present invention;

Fig. 2 is a magnified, partial perspective view of FIG. 1 in a first, non-expanded form, illustrating the polymeric surface coating selectively applied to wire members;

15

Fig. 3 is a magnified, partial perspective of FIG. 2 in a second, expanded form, illustrating the polymeric fragmentation and subsequent elution of a therapeutic substance arising from the expansion of the stent;

Fig. 4 is a schematic representation of a catheter of the present invention having a folded balloon in a first position thereon inserted within a vessel lumen; and

20

Fig. 5 is a schematic representation of the catheter of Fig. 4 having the balloon in a second expanded position for treatment of the vessel wall.

Detailed Description of the Drawings

Stents of the type shown in Fig. 1, disclosed in U.S. Patent Application Serial No. 08/874,190, filed June 13, 1997, entitled "Polymeric Layered Stents", perform the desired applications of dilating and maintaining the patency of various lumen passages within the 5 human body. The above application is assigned to the assignee of the present invention, and the disclosure is hereby incorporated by reference.

Referring now to the drawings wherein like reference numerals refer to like elements throughout the several views, Fig. 1 shows a perspective view of a stent 10, in a non-expanded form, in accordance with the present invention. The skeletal frame of the 10 stent 10 preferably includes wire-like members 12 forming a distinct, repetitive serpentine pattern. This repetitive serpentine pattern consists of multiple U-shaped curves 14. These U-shaped curves 14 form interstitial spaces 16. With no recognizable beginning or end to this serpentine pattern, wire 12 forms expandable serpentine element 18. Serpentine elements 18 are arranged along the longitudinal axis of the stent 10 so 15 that the U-shaped curves 14 of abutting serpentine elements 18 may be joined through an interconnecting element 20. Through the interconnecting elements 20, a continuous wire 12 framework is created between multiple serpentine elements 18 forming the stent 10.

A surface treatment 30 is selectively applied to the skeletal frame of the stent 10. This surface treatment 30 comprises at least two overlying coatings selectively applied to 20 at least a portion of the exterior surface of the wire-like members 12. The function of the two overlying coatings is best understood from the depictions in Fig. 2 and Fig. 3, as described below.

Referring now to Fig. 2, a portion of the stent of Fig. 1 is depicted in magnified view with the first coating 32 disposed over at least a portion of the exterior surface of wire-like members 12. The first coating 32 includes at least in part, a therapeutic substance or drug. In a preferred embodiment, the therapeutic substance is comprised, at 5 least in part, of an anti-proliferative or anti-angiogenic drug. This therapeutic substance is typically dispersed and contained in a polymeric carrier matrix forming the first coating 32. The use of a matrix allows for a selectively controlled elution rate for the incorporated drug or therapeutic substance. By modifying the ratio of polymeric carrier to therapeutic substance, the ability of the therapeutic substance to elute from the carrier 10 either increases or decreases. In a further preferred embodiment, the elution rate of the therapeutic substance may be controlled by utilizing a biodegradable polymeric carrier. Polylactic acid (PLA), polyglycolic acid, polyethylene oxide (PEO), polycaprolactone are examples of such polymeric carriers. Either the homopolymer or the copolymer forms of these materials may be utilized in the incorporation with the therapeutic 15 substance. Other polymeric carriers which may be utilized include: polyurethane, polysiloxane, polyacrylate and their mixtures or copolymers.

Other therapeutic substances or drugs can also be incorporated into the first coating, either alone or in combination with the anti-proliferative or anti-angiogenic agents. These drugs can include heparin, antibiotics, radiopaque agents and anti- 20 thrombogenic agents.

These components may be added to the anti-proliferative or anti-angiogenic drug in order to alter the function of the therapeutic substance. In a preferred embodiment, to prevent the aggregation of platelets, fibrin, clotting factors, and cellular elements of the

blood as a result of the implementation of the stent 10, the anti-proliferative drug or anti-angiogenic drug may also contain an additional anti-thrombogenic drug that may be incorporated with the other drugs forming the first coating 32. In a further preferred embodiment, the anti-angiogenic drug is Taxol, Taxol derivatives, colchicine, vinblastine, 5 or epothilone.

The second coating 34, preferably the outermost coating, overlays at least a substantial portion of the first, or previous coating 32. This second coating 34 comprises a material that is generally impervious to the elution of the therapeutic substance or drug incorporated in the first coating 32. The second coating 34 acts as a protective coating 10 for the drug or therapeutic substance which prevents the drug or therapeutic substance from elution prior to proper placement within the vessel lumen at a treatment site. Further, this protective layer prevents physical damage to the drug coating layer during 15 insertion. In preferred embodiments, release of the therapeutic substance is enhanced by contact with water or other liquids present in the blood or other body lumen. This is particularly true in embodiments which incorporate a drug or therapeutic substance which 20 is water soluble or a polymeric carrier that is hydrophilic and tends to release more therapeutic substance upon contact with a liquid such as water. Thus, the second coating 34 or overlayer of protective coating is preferably impervious to water or body fluids, at least for the time period required for placement of the stent within the vessel lumen at the treatment site. In this way, the elution of the drug is prevented until the medical device or stent is located at the required treatment site.

Thus, in use, the stent or other medical device of the present invention is coated with first a drug or therapeutic substance, followed by an overlying coat of a second

coating or protective coating. The first coating may be placed on the medical device while in an unexpanded configuration, or alternatively, the device may be expanded for coating and then contracted for placement in the vessel. The second coating, or protective coating, is made to overlie the first coating while the medical device is in the 5 first position for insertion in the lumen. In preferred embodiments, the second coating material is relatively inelastic so that the second coating fractures during expansion of the body portion of the medical device to the second position. The portion of the stent depicted in Fig. 2 is depicted in Fig. 3 in an expanded state, which clearly indicates a multiplicity of fractures or fissures 40 throughout the second coating 32 with the drug or 10 therapeutic substance 30 eluting through the fissures 40.

As previously stated, the second coating is preferably a polymeric coating which is relatively inelastic so that the expansion of the stent or other medical device causes fractures to form within the coating surface. These fractures allow the elution of the drug or therapeutic substance therethrough. A preferred polymeric material includes 15 polylactic acid, polyglycolic acid, polyanhydrides, polyphosphazene or poly(orthoester). The thickness of the second coating is preferably about 0.01 μ m to about 5.0 μ m. The second coating is preferably biodegradable or bioabsorbable so that over time the second coating is absorbed by the body.

The present invention has been discussed in conjunction with a preferred stent. 20 However, it is recognized that the invention disclosed herein may be utilized with any stent design which is expanded from a first position to a second position with resultant fracture of a second protective coating thereon. Preferred stents include those generally tubular structures having an exterior surface defined by a plurality of interconnected

struts having interstitial spaces therebetween. In the first position, the stent is sized so that it may be inserted into the lumen of the intravascular system. Once located at a point of treatment, the stent may be expanded to a second position wherein at least a portion of the exterior surface contacts the wall of the vessel lumen.

5 The use of a second protective coating, as described above for a stent, can also be incorporated into a medical device such as a balloon-type drug delivery catheter or balloon dilatation catheter. Figs. 4 and 5 depict the incorporation of the present invention into a balloon catheter design. The materials and therapeutic substances discussed above are equally applicable in the present balloon catheter embodiment.

10 Now referring to Fig. 4, a vessel 50 within the vascular system is depicted schematically with a lumen 52 defined therethrough which is partially occluded by a stenosis 54 therein. The lumen is defined by lumen walls 56 as indicated. A balloon catheter 58 is depicted as being inserted into the vessel lumen 52. The balloon catheter 58 includes a shaft 60 having disposed on a distal portion thereof an inflatable balloon 62.

15 The balloon 62 is depicted in a folded or uninflated profile which is suitable for inserting into the lumen 52 of the blood vessel 50.

16 The balloon 62 includes a drug or therapeutic substance coated on the surface thereof. In preferred embodiments, the entire surface of the balloon is coated with a drug or therapeutic substance, either alone or in a polymeric carrier, while the balloon is in an inflated position so that the entire surface thereof includes the drug or therapeutic substance thereon. The second coating or protective coating is applied while the balloon is in a deflated or low profile condition. Again, this protective coating prevents the

elution of the drug from the surface of the balloon which is exposed during insertion of the catheter prior to inflation of the balloon at the treatment site.

Referring now to Fig. 5, the balloon catheter 58 of Fig. 4 is depicted with the balloon located across the stenotic area 54 in an inflated condition. As shown in Fig. 5, 5 the balloon includes a first coat 30, which includes the drug or therapeutic substance, and a second coat, which is the protective coating which was applied when the balloon was in a deflated condition. Fig. 5 schematically depicts the multiplicity of fissures 40 which are formed in the balloon surface coating 32 upon expansion of the balloon. This results in elution of the drug or therapeutic substance 30 through such fissures into the treatment 10 area.

Numerous characteristics and advantages of the invention covered by this document have been set forth in the foregoing description. It will be understood, however, that this disclosure is, in many aspects, only illustrative. Changes may be made in details, particularly in matters of shape, size, and arrangement of parts without 15 exceeding the scope of the invention. The invention scope is defined, of course, in the language within the appended claims are expressed.

What is claimed is:

1. A medical device for treating a lumen wall comprising:

a body portion having an exterior surface defined thereon, said body portion being expandable from a first position, wherein said body portion is sized for insertion into said lumen, to a second position wherein at least a portion of said exterior surface is in contact with said lumen wall;

a first coating disposed over at least a portion of said exterior surface of said body portion, said first coating comprising at least in part a therapeutic substance; and,

a second coating overlying at least a substantial portion of said first coating, said second coating comprising a material that is generally impervious to elution of said therapeutic substance therethrough when said body portion is in said first position when inserted in said lumen, while being relatively inelastic so that said second coating fractures during expansion of said body portion to said second position to allow elution of said therapeutic substance through fissures formed therethrough.

2. The medical device of claim 1, wherein said device is an expandable stent.

3. The medical device of claim 1, wherein said device is a balloon catheter.

4. The medical device of claim 1, wherein said therapeutic substance releases from said exterior surface in response to fluid contact absent said second coating.

5. The medical device of claim 1, wherein said therapeutic substance is selected from the group consisting of : heparin, antibiotics, radiopaque agents, anti-thrombogenic agents, anti-proliferative agents, anti-angiogenic agents and combinations thereof.
6. The medical device of claim 5, wherein said anti-proliferative and anti-angiogenic agents are selected from the group consisting of: taxol, taxol derivatives, colchicine, vinblastine or epothilone.
7. The medical device of claim 4, wherein said fluid contact includes blood within said lumen.
8. The medical device of claim 1, wherein said first coating further comprises a polymeric carrier having said therapeutic substance dispersed therethrough.
9. The medical device of claim 8, wherein said polymeric carrier is biodegradable.
10. The medical device of claim 9, wherein said polymeric carrier is selected from the group consisting of: polylactic acid, polyglycolic acid, polyethylene oxide, polycaprolactone, polydioxanones, polyanhydrides, polyphosphazenes, poly(orthoesters) and mixtures or copolymers thereof.

11. The medical device of claim 1, wherein said second coating is a polymeric material selected from the group consisting of: polylactic acid, polyglycolic acid, polyanhydrides, polyphosphazenes, poly(orthoesters) and mixture and copolymers thereof.

12. The medical device of claim 11, wherein said second coating of a thickness of about 0.01 μ m to about 5.0 μ m.

13. An intravascular stent adapted for treating a vessel wall comprising:

a generally tubular structure having an exterior surface defined by a plurality of interconnected struts having interstitial spaces therebetween, said generally tubular structure expandable from a first position, wherein said stent is sized for intravascular insertion, to a second position, wherein at least a portion of said exterior surface contacts said vessel wall, said expanding of said generally tubular structure accommodated by flexing and bending of said interconnected struts;

a first coating disposed over at least a portion of said exterior surface of said generally tubular structure, said first coating comprising at least in part a therapeutic substance; and,

a second coating overlying at least a substantial portion of said first coating, said second coating comprising a material that is generally impervious to elution of said therapeutic substance therethrough when said body portion is in said first position within said intravascular lumen, while being relatively inelastic so that said second coating fractures in response to flexing and bending of said struts during expansion to said second

position to allow elution of said therapeutic substance through fissures formed therethrough.

14. The stent of claim 13, wherein said therapeutic substance releases from said exterior surface in response to fluid contact absent said second coating.

15. The stent of claim 13, wherein said therapeutic substance is selected from the group consisting of : heparin, antibiotics, radiopaque agents, anti-thrombogenic agents, anti-proliferative agents, anti-angiogenic agents and combinations thereof.

16. The stent of claim 15, wherein said anti-proliferative and anti-angiogenic agents are selected from the group consisting of: taxol, taxol derivatives, colchicine, vinblastine and epothilone.

17. The stent 14, wherein said fluid contact includes blood within said lumen.

18. The stent of claim 13, wherein said first coating further comprises a polymeric carrier having said therapeutic substance dispersed therethrough.

19. The stent of claim 18, wherein said polymeric carrier is biodegradable.

20. The stent of claim 19, wherein said polymeric carrier is selected from the group consisting of: polylactic acid, polyglycolic acid, polyethylene oxide,

polycaprolactone, polydioxanone, polyanhydrides, polyphosphaenes, poly(orthoesters) and mixtures or copolymers thereof.

21. The stent of claim 13, wherein said therapeutic substance is elutable in contact with water containing fluids absent said second coating.

22. In an intravascular medical device having a body portion with an exterior surface defined thereon, at least a portion of said body portion which is expandable from a folded or unexpanded first position, which is adapted for insertion into a vascular lumen to an expanded second position, which is adapted for treatment of the vascular lumen wall by contact with at least a portion of said exterior surface, the improvement comprising:

a first coating disposed over at least a portion of said exterior surface of said body portion, said first coating comprising at least in part a therapeutic substance; and,

a second coating overlying at least a substantial portion of said first coating, said second coating comprising a material that is relatively inelastic so that said second coating fractures during expansion of said body portion to said second position to allow elution of said therapeutic substance through fissures formed therethrough.

23. The intravascular medical device of claim 22, wherein said therapeutic substance releases from said exterior surface in response to fluid contact absent said second coating.

24. The intravascular medical device of claim 22, wherein said therapeutic substance is selected from the group consisting of : heparin, antibiotics, radiopaque agents, anti-thrombogenic agents, anti-proliferative agents, anti-angiogenic agents and combinations thereof.

25. The intravascular medical device of claim 24, wherein said anti-proliferative and anti-angiogenic agents are selected from the group consisting of: taxol, taxol derivatives, colchicine, vinblastine and epothilones.

26. The intravascular medical device of claim 22, wherein said first coating further comprises a polymeric carrier having said therapeutic substance dispersed therethrough.

27. The intravascular medical device of claim 26, wherein said polymeric carrier is biodegradable.

28. The intravascular medical device of claim 27, wherein said polymeric carrier is selected from the group consisting of: polylactic acid, polyglycolic acid, polyethylene oxide, polycaprolactone, polydioxanone, polyanhydrides, polyphosphazenes, poly(orthoesters) and mixtures or copolymers thereof.

29. The intravascular medical device of claim 22, wherein said therapeutic substance is elutable in contact with water containing fluids absent said second coating.

30. A catheter for drug delivery comprising:

a longitudinally extending shaft having a distal end and a proximal end, the shaft defining an inflation lumen;

a balloon member having an exterior surface defined thereon disposed proximate the distal end of said shaft in fluid communication with said inflation lumen, said balloon member expandable from a first deflated position, wherein said balloon member is sized for intravascular insertion, to a second inflated position, wherein at least a portion of said exterior surface contacts said vessel wall;

a first coating disposed over at least a portion of said exterior surface of said balloon member, said first coating comprising at least in part a therapeutic substance; and,

a second coating overlying at least a substantial portion of said first coating, when said balloon member is in said first deflated position, said second coating comprising a material which is relatively inelastic so that said second coating fractures in response to expansion of said balloon member to said second position to allow elution of said therapeutic substance through fissures formed therethrough.

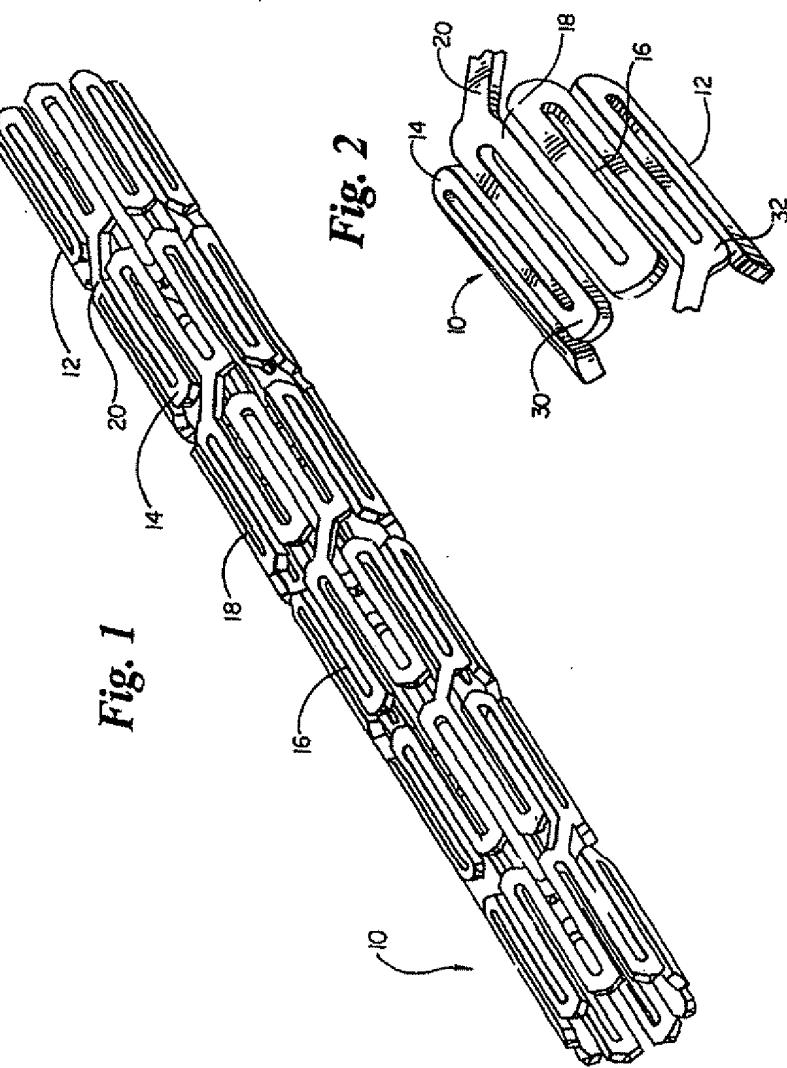
31. The catheter of claim 30, wherein said therapeutic substance releases from said exterior surface in response to fluid contact absent said second coating.

32. The catheter of claim 30, wherein said second coating is a polymeric material selected from the group consisting of polylactic acid, polyglycolic acid,

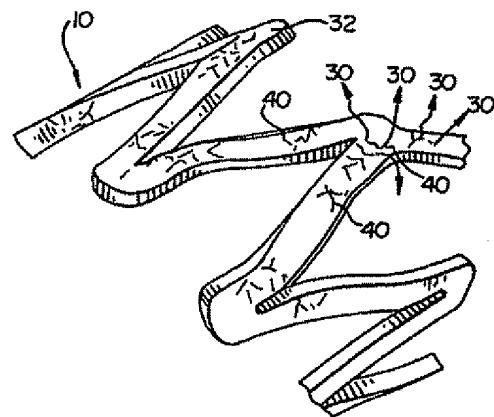
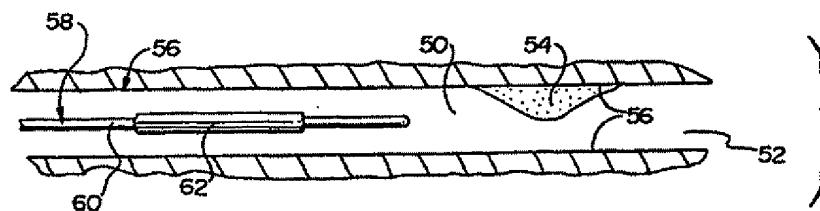
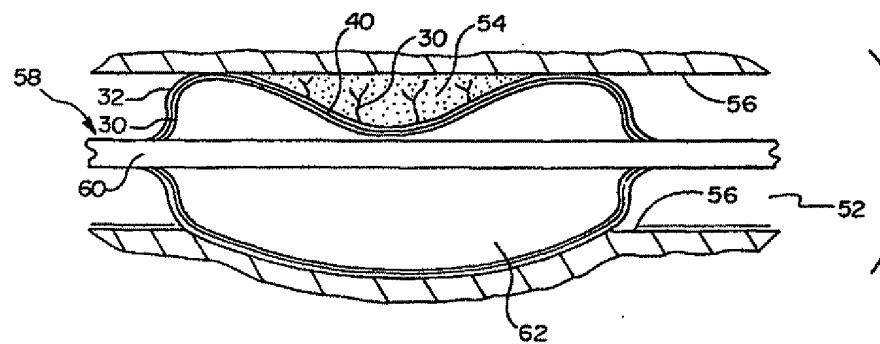
polyanhydrides, polyphosphazenes, poly(orthoesters) and mixtures and copolymers thereof.

33. The catheter of claim 30, wherein said therapeutic substance is selected from the group consisting of: taxol, taxol derivatives, colchicine, vinblastine and epothilone.

34. The catheter of claim 30, wherein said therapeutic substance is elutable in contact with water containing fluids absent said second coating.



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Fig. 3**Fig. 4****Fig. 5**

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/00717

A. CLASSIFICATION OF SUBJECT MATTER:
IPC 7 A61F2/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 324 261 A (AMUNDSON RODNEY R ET AL) 28 June 1994 (1994-06-28) figures 4,5 column 2, line 51 -column 3, line 2 column 3, line 40 -column 4, line 32 column 4, line 41 -column 6, line 27 claims 1-8	1,3-12, 22-34
A	—	13-21
Y	US 5 735 897 A (BUIRGE ANDREW W) 7 April 1998 (1998-04-07) column 2, line 37 -column 3, line 45 column 4, line 6 - line 31 column 5, line 26 - line 54 claims 1-58	13
A	—	1,22,30
	—	—/—

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search:

16 May 2000

Date of mailing of the international search report

26/05/2000

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INTERNATIONAL SEARCH REPORT

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PCT/US 00/00717

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 23228 A (ALZA CORP) 4 June 1998 (1998-06-04) page 6, line 30 -page 8, line 4 page 10, line 1 - line 23 page 13, line 3 -page 14, line 2	13
A		1, 22, 30
A	US 5 674 241 A (BLEY ROBERT S ET AL) 7 October 1997 (1997-10-07) column 5, line 63 -column 7, line 62	1, 13, 22, 30

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/US 00/00717

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
US 5324261	A	28-06-1994	US 5102402 A US 5370614 A CA 2077539 A DE 69119753 D DE 69119753 T EP 0519063 A IE 78821 B JP 5505132 T WO 9211890 A US 5893840 A	07-04-1992 06-12-1994 05-07-1992 27-06-1996 23-01-1997 23-12-1992 25-02-1998 05-08-1993 23-07-1992 13-04-1999
US 5735897	A	07-04-1998	WO 9510989 A	27-04-1995
WO 9823228	A	04-06-1998	AU 5266698 A	22-06-1998
US 5674241	A	07-10-1997	US 5968070 A AU 4929696 A CA 2213403 A EP 0810845 A WO 9625897 A	19-10-1999 11-09-1996 29-08-1996 10-12-1997 29-08-1996